A Detailed Study on Mathematics Involved in CANCER Spread and its Treatment.

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Abstract: In this Paper, we present and analyze various types of Cancer spread and how they can be interpreted by using concepts of Mathematics. We also investigate Mathematical models developed to explain the cancer treatment methods. Furthermore, we discuss the role of differential equations at different stages of treatment methods. We also discuss the role of exponential decay functions in cycle specific chemotherapy, which remains one of the best ways to treat cancer.

Key words: Mathematical Concepts, Cancer Spread, Treatment, Chemotherapy, Mathematical models, Differential equations, Cycle Specific Chemotherapy, Exponential decay functions.

Introduction: Mathematics provides a systematic approach in solving problems. Mathematical biology aims to mathematically represent and model biological processes, using techniques and tools of applied mathematics. Mathematical models have been important for understanding various areas of biology. Due to the complexity of living systems, theoretical biology employs diverse fields of mathematics and has advanced new techniques.

Cancer is a disease that results when cellular changes cause the uncontrolled growth and division of cells. Cancer cells differ from normal cells in many ways. They grow in the absence of signals telling them to grow, while normal cells only grow when they receive such signals. Cancer cells ignore the normal mechanisms that tell cells to stop dividing or to die. Additionally, they invade nearby areas and spread to other parts of the body, in contrast to normal cells that stop growing when they encounter other cells and do not typically move around the body. Cancer cells also hide from the immune system and trick it into helping them stay alive and proliferate. Furthermore, they accumulate changes in their chromosomes, such as duplications and deletions, and some

have double the normal number of chromosomes. Cancer cells rely on different kinds of nutrients than normal cells and some generate energy from nutrients in a unique way, allowing them to grow more quickly. Often, cancer cells depend so heavily on these abnormal behaviors that they cannot survive without them. Researchers have exploited this fact by developing therapies that target the distinctive features of cancer cells. For instance, some cancer treatments prevent blood vessels from growing towards tumors, essentially starving the tumor of the nutrients it needs.

Mathematics in Spread of Cancer Cells:

Cancer growth can be explained through mathematical models in three different ways [1].

1. Exponential growth
2. Logistic Growth
3. Gompertz model growth

Exponential growth: A differential equation can be used to model the growth of tumor, provided that

$$Initial\ population\ of\ cell\ population = N_0;$$

$$Growth\ function = F, a\ positive\ valued\ function.$$

Where F describes the increase per unit time in tumor cell population.

This leads to the following model of tumor growth:

$$N'(t) = F(N)$$

$$N(0) = N_0$$

The exponential model of tumor growth is obtained by assuming that the doubling time is constant.

$$N'(t) \propto N$$

$$N'(t) = \lambda_E N$$

Where λ_E is a constant that is equal to proportional increase in the tumor cell population per unit time.

$$\frac{dN}{dt} = \lambda_E N$$

separating the variables and integrating,

$$\int \frac{dN}{N} = \int \lambda_E \, dt$$

$$\ln N = \lambda_E t + \ln N_0$$

$$N = N_0 e^{\lambda_E t}$$

Take $t = \tau$ *as the doubling time,*

$$2N_0 = N_0 . e^{\lambda_E \tau}$$

$$ln2 = \lambda_E \tau$$

$$\lambda_E = \frac{ln2}{\tau}.$$

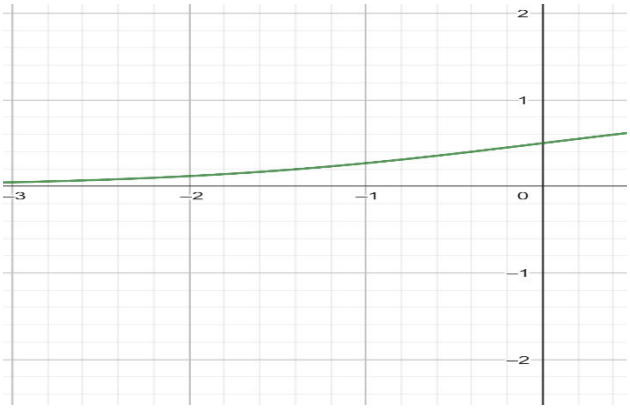
Researchers have found that for certain cancers, as the tumor mass grows, its growth rate declines due to a reduction in the tumor's growth fraction. Therefore, this cannot be reproduced using exponential model.

The other two models of Tumor Growth: Logistic and Gompertz [1]

These models describe tumor growth with a decreasing growth rate as tumor mass increases. This pattern is characteristic of sigmoidal growth

functions, where the tumor mass eventually stabilizes at a plateau population over time. The standard equation for a sigmoidal function is presented, along with its corresponding graph.

The standard equation of sigmoidal function is given by: $f(x) = \frac{1}{1+e^{-x}}$



The logistic growth function is:

$$N'(t) = \lambda_L N[1 - \frac{N}{\theta}]$$

Where λ_L is a positive constant.

The exponential and logistic growth models produce similar results until the tumor burden approaches the carrying capacity of the system.

$$N(t) = \frac{\theta}{1 + e^{-\lambda_L t}(\frac{\theta - N_0}{N_0})}$$

The parameter λ_L can be calculated from the tumor doubling time by rearranging terms above,

$$\lambda_L = \frac{1}{\tau} \ln [\frac{\theta - N_0}{\frac{\theta}{2} - N_0}]$$

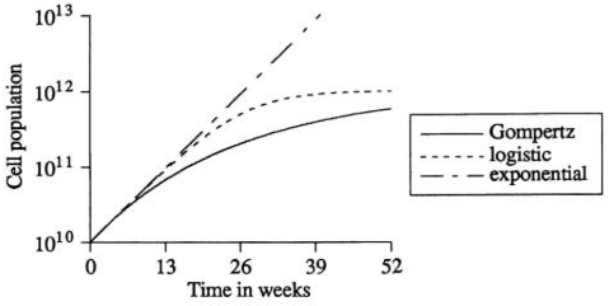
Gompertz Model:

The Gompertz differential equation is given by:

$$N'(t) = \lambda_G N \ \ln (\frac{\theta}{N})$$

Where the parameter λ_G is a positive constant.

The Gompertz equation gave the best fit in four of the five tumor cell populations. The graphical representation of above three models is given by:



Three growth models Gompertz [1], Logistic and exponential are used here to simulate tumor growth. For all three models, the initial tumor burden is 10^{10} cells and the initial tumor population doubling time is 4 weeks. The plateau population for the Gompertz and logistic model is $\theta = 10^{12}$ cells. The logistic and exponential growth histories are the same until the tumor burden comes with in an order of magnitude of the plateau population.

Treatment of Cancer: "Those diseases that medicine cannot cure are cured with knife. Those that knife cannot cure are cured by fire. Those that fire

cannot cure are considered incurable". Was stated by Hippocrates almost 2.500 years ago. Many have used this quote as one of the earliest descriptions of using heat to treat cancer.

Cancer treatment in ancient times differed significantly from modern approaches. While the understanding of cancer as a disease was limited, various methods were employed:

- **Ancient Egypt (1600 BC):**

  (How Was Cancer Treated in Ancient Greece? 2023) notes the earliest documented cases of cancer, including breast cancer, originating in ancient Egypt. (Sudhakar, 2009) [2] adds that surgical removal of surface tumors was practiced, similar to modern techniques. However, (Sudhakar, 2009) [2] also mentions that treatment was primarily palliative, focusing on relieving symptoms rather than curing the disease.

- **Ancient Greece (460-370 BC):** (Sudhakar, 2009) [2] mentions the use of arsenic pastes in ancient Egypt and credits Hippocrates (460-370 BC) with coining the term "cancer". (How Was Cancer Treated in Ancient Greece?, 2023) [3] elaborates on Hippocrates's humoral theory, which attributed cancer to an excess of black bile. Treatments likely focused on restoring the balance of humors.

- **Surgery:** Surgical removal of tumors was practiced in some ancient cultures, as evidenced by (Sudhakar, 2009) [2] 's mention of tumor removal in ancient Egypt.

- **Other Methods:** Other ancient practices likely involved herbal remedies and other traditional medicine approaches, though detailed records are scarce.

It's important to note that ancient cancer treatments were based on limited understanding of the disease. (History of Cancer, 2023) highlights the evolution of cancer understanding, from early theories of contagious poison to the later discovery of metastasis using microscopes. The development of modern cancer treatments has been a long process, building upon centuries of scientific advancements.

The choice of cancer treatment depends on the specific type and stage of the disease, but typical approaches include: surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy (Bortfeld et al.) [4] (West et al.) (Benzekry et al.) [5].

Mathematical modeling can play an important role in optimizing cancer treatment. Models have been developed to study tumor growth dynamics and the effects of different therapies, such as by incorporating factors like tumor repopulation rate, hypoxia, and the immune response. (Benzekry et al.) [5] (Bortfeld et al.) [4]

(Stability Analysis of Switched Systems for Cancer Treatment by Anti-Angiogenesis via Minimum Dwell Time (MDT)) For example, optimal radiation therapy fractionation schedules can be determined using control theory and dynamic programming to maximize tumor cell kill while minimizing toxicity to healthy tissue. (Bortfeld et al.) [4] Additionally, models of switched systems have been used to study cancer therapy strategies that alternate between different treatment modalities to exploit their synergistic effects.

(Stability Analysis of Switched Systems for Cancer Treatment by Anti-Angiogenesis via Minimum Dwell Time (MDT))

Overall, mathematics offers powerful tools for advancing our understanding of cancer biology and improving the design of effective cancer treatments. (Benzekry et al.) [5] (Bortfeld et al.) [4] (Zaider et al.)

Surgery: (Krzyszczyk et al.) [6] mentions surgery as an option for solid tumors that haven't metastasized and are accessible. It aims to remove the cancerous tissue.

Surgery is often combined with other treatments like chemotherapy or radiation therapy. (Chen et al., 2020)(McEntee, 1995)(Treatment with Kerosene: Reviews, 2022) It can debulk the tumor, making other therapies more effective. Surgery is an invasive procedure with potential risks like infection, bleeding, and complications related to anesthesia. (Parekh & Iannettoni, 2007) [7] (Chen et al., 2020)Surgery isn't suitable for all cancers, especially those that have metastasized widely or are located in inaccessible areas. (Parekh & Iannettoni, 2007) [7](Chen et al., 2020).Surgical recovery can be lengthy and painful, impacting the patient's ability to resume normal activities. (Parekh & Iannettoni, 2007) [7].The prospect of surgery can be emotionally distressing for patients. (Parekh & Iannettoni, 2007) [7]

Side Effects: Depending on the location and extent of the surgery, there can be long-term side effects, such as functional impairments or cosmetic changes.(Augmentation Mammoplasty. Advantages and Disadvantages of Breast Prostheses, 2023) discusses some of these in the context of breast augmentation, though the specific side effects vary greatly depending on the type of cancer surgery.

Conclusion: The decision to pursue surgery is made on a case-by-case basis, considering the type and stage of cancer, the patient's overall health, and their preferences. It's essential to discuss the benefits and risks with a healthcare professional to make an informed decision.

Radiation Therapy: (Krzyszczyk et al.) [6] also notes radiotherapy, which uses high doses of radiation to kill cancer cells and shrink tumors. It works by damaging the DNA of cancer cells,

preventing them from growing and dividing.

Drawbacks: These can include fatigue, skin irritation (like sunburn), hair loss in the treated area, and nausea. (Radio Frequency Ablation Procedure in India, 2023) mentions the use of local anesthetic and mild sedative to reduce discomfort during procedures like radiofrequency ablation, a type of radiotherapy. Depending on the area treated, long-term effects can include fibrosis (tissue scarring), lymphedema (swelling), and secondary cancers. (Mahantshetty et al., 2014) mentions high complication rates in some re irradiation series. (Tighten Your Skin with Our Intragen Treatments, 2022) mentions the high cost associated with some systems, particularly those involving fractional microneedle radiofrequency devices. RFA, for instance, is not recommended for people with active infections or bleeding problems. (Radio Frequency Ablation Procedure in India, 2023) advises discussing suitability with a doctor. Other procedures may have limitations related to the size or location of the tumor.

Conclusion: It's crucial to discuss the benefits and risks of radiotherapy with your doctor to make an informed decision. They can explain the specific procedures involved and address any concerns you may have.

Chemotherapy: (Krzyszczyk et al.) [6] mentions chemotherapy, which uses drugs to kill cancer cells. (Cancer Treatments) and (Sharma et al.) also highlight chemotherapy as a common cancer treatment. While it can be effective, it also has potential drawbacks.

Chemotherapy can be administered in various ways:

Intravenously: This is the most common method, where the drugs are injected into a vein. (2023) notes that the duration and frequency depend on the patient's condition.

Orally: Some chemotherapy drugs are taken as pills. (Oral Chemotherapy Treatment, 2019) mentions that the dosage of oral chemotherapy varies depending on the type of cancer.

Injection: Drugs can be injected directly into a muscle, under the skin, or into the cerebrospinal fluid.

Topically: Creams containing chemotherapy drugs can be applied directly to the skin for certain types of skin cancer.

Chemotherapy is often given in cycles, with periods of treatment followed by rest periods to allow the body to recover. (Oral Chemotherapy Treatment, 2019) advises consulting a cancer hospital for clear dosage instructions. The specific drugs and treatment schedule depend on the type and stage of cancer, the patient's overall health, and other factors.

Drawbacks: Chemotherapy can cause a range of side effects due to its impact on rapidly dividing cells, including healthy ones: These can include nausea and vomiting, hair loss, fatigue, mouth

sores, and an increased risk of infection. (Zeng et al., 2023) notes that chemotherapy can cause nausea, vomiting, fever, respiratory distress, bone marrow suppression, and hair loss. Some chemotherapy drugs can cause more serious side effects, such as heart damage, kidney damage, nerve damage, and secondary cancers. (Ding et al., 2016) mentions that chemotherapy can harm healthy cells and cause severe side effects. Cancer cells can sometimes develop resistance to chemotherapy drugs, making the treatment less effective. (Yang et al., 2020) highlights that chemotherapy resistance is a major challenge and causes most treatment failures. The side effects of chemotherapy can significantly impact a patient's quality of life, making it difficult to perform daily activities. (Zeng et al., 2023) points out that these complications can reduce treatment adherence and affect patients' quality of life.

Conclusion: It's essential to have a thorough discussion with your oncologist about the potential benefits and risks of chemotherapy. They can explain the specific treatment plan and address any concerns you may have. (Chemo-Treatment in Bangalore, 2023) emphasizes the importance of regular chats with the oncologist to manage anxiety related to cancer treatment.

Targeted Therapy: Targeted therapy is a type of cancer treatment that targets specific molecules involved in cancer cell growth and spread. Unlike chemotherapy, which affects all rapidly dividing cells, targeted therapy aims to be more precise, potentially leading to fewer side effects.

Treatment: Targeted therapies work by interfering with specific molecules that play a role in cancer development. (Min & Lee, 2022) describes targeted therapy as focusing on signal transduction inhibitors. These therapies can:

- **Inhibit growth signals:** Some targeted therapies block signals that tell cancer cells to grow and divide. (Sorafenib, 2024) mentions Sorafenib, a targeted therapy that inhibits multiple kinases involved in tumor growth and angiogenesis.
- **Promote cell death:** Other targeted therapies promote apoptosis, the process of programmed cell death, in cancer cells. (Imatinib, 2024) discusses Imatinib, a targeted therapy that induces apoptosis in certain cancer cells.
- **Block angiogenesis:** Some therapies prevent the formation of new blood vessels that supply tumors with nutrients and oxygen, thus hindering their growth. (Sorafenib, 2024) notes that Sorafenib also has anti-angiogenic properties.
- **Boost the immune system:** Certain targeted therapies help the immune system recognize and destroy cancer cells. (Ipilimumab (Anti-CTLA-4),

2024) describes Ipilimumab, which targets CTLA-4, a protein that normally suppresses immune responses.

Targeted therapies are often administered orally or intravenously. The specific treatment regimen depends on the type of cancer, the specific targeted therapy used, and the patient's overall health.

Drawbacks: While targeted therapies generally have fewer side effects than traditional chemotherapy, they can still cause adverse reactions: Common side effects can include skin rashes, diarrhea, high blood pressure, and fatigue. (Min & Lee, 2022) acknowledges that while targeted therapy aims for specificity, it's not completely without side effects. The specific side effects depend on the particular drug used. Similar to chemotherapy, cancer cells can develop resistance to targeted therapies over time, making them less effective. (Min & Lee, 2022) mentions that despite the benefits, targeted therapy faces challenges like drug resistance, leading to the pursuit of personalized medicine. Targeted therapies can be expensive, and insurance coverage may vary. Targeted therapies are only effective against cancers that express the specific molecular targets they are designed to attack. (Olivo et al., 2010) notes that targeted therapies are designed for specific molecular pathways, making them unsuitable for all cancers. Molecular testing is often necessary to determine if a patient's tumor is likely to respond to a particular targeted therapy.

Conclusion: It's crucial to discuss the potential benefits and risks of targeted therapy with your oncologist. They can help determine if targeted therapy is appropriate for your specific situation and explain the potential side effects and other considerations

Hormonal Therapy: Hormonal therapy, also known as endocrine therapy, is used to treat cancers that are sensitive to hormones, such as some breast and prostate cancers. It works by blocking or reducing the effects of hormones that fuel the growth of these cancers.

Treatment: Hormonal therapy can be administered in several ways:

Drugs that block hormone production: These drugs prevent the body from making certain hormones. For example, in postmenopausal women with breast cancer, aromatase inhibitors (Santoro, 2015) reduce estrogen production. (Sandow, 1983) discusses the use of LHRH (luteinizing hormone-releasing hormone) agonists, which initially stimulate but then suppress pituitary and gonadal hormone production, leading to a reversible inhibition useful in treating hormone-dependent tumors like breast and prostate cancer.

Drugs that block hormone receptors: These drugs prevent hormones from binding to receptors on cancer cells, thus blocking their growth-promoting effects. (Sandow, 1983) mentions the

use of LHRH analogues in treating hormone-dependent tumors.

Surgery to remove hormone-producing organs: In some cases, the ovaries or testes may be surgically removed to reduce hormone levels.

The specific type of hormonal therapy and treatment duration depend on factors such as the type and stage of cancer, the patient's age and menopausal status, and other individual factors.

Drawbacks: While hormonal therapy can be effective, it can also cause side effects: In women, hormonal therapy can cause hot flashes, night sweats, vaginal dryness, and mood swings, similar to menopause. (Santoro, 2015) discusses the management of menopausal symptoms, noting that some alternative treatments like yoga, omega-3 fatty acid supplementation, and black cohosh have been found ineffective. Other potential side effects can include fatigue, weight gain, bone loss, and an increased risk of blood clots. (Hench et al., 1957) mentions the importance of considering both the benefits and potential disadvantages of hormonal treatment, especially for long-term use, and emphasizes the concept of "hypercortisonism" to represent the calculated risk. Hormonal therapy is only effective for hormone-sensitive cancers. (Sandow, 1983) specifies that the clinical applications of high-dose LHRH agonist suppression are for precocious puberty and hormone-dependent tumors. Long-term use of some hormonal therapies may increase the risk of certain health problems, such as heart disease or osteoporosis. (Hench et al., 1957) discusses the diagnosis, treatment, and prevention of chronic hypercortisonism in patients with rheumatoid arthritis, highlighting the need for careful consideration of long-term hormonal treatment.

Conclusion: It's essential to discuss the potential benefits and risks of hormonal therapy with your doctor. They can help determine if hormonal therapy is appropriate for your specific situation and explain the potential side effects and other considerations.

Immunotherapy: Immunotherapy harnesses the body's own immune system to fight cancer. It can boost the immune system's natural ability to recognize and destroy cancer cells or train it to specifically target cancer cells.

Treatment: Several types of immunotherapy exist:

Immune checkpoint inhibitors: These drugs block proteins that normally keep the immune system in check, allowing it to attack cancer cells more aggressively. (Ipilimumab (Anti-CTLA-4), 2024) describes Ipilimumab, an immune checkpoint inhibitor that targets CTLA-4.

Adoptive cell transfer: This involves removing immune cells from the patient, modifying them in the laboratory to enhance their cancer-fighting abilities, and then infusing them back into the patient.

Therapeutic vaccines: These vaccines help the immune system recognize and target specific cancer cells.

Monoclonal antibodies: These laboratory-produced antibodies target specific proteins on cancer cells, marking them for destruction by the immune system.

The specific type of immunotherapy and treatment schedule depend on the type of cancer, the patient's overall health, and other factors.

Drawbacks: While immunotherapy can be highly effective, it can also cause side effects, which are often related to the immune system's increased activity. These can range from mild skin rashes and diarrhea to more serious inflammation of organs like the lungs, liver, or intestines. (Ipilimumab (Anti-CTLA-4), 2024) mentions potential immune-related adverse events associated with Ipilimumab. Immunotherapy is not effective for all types of cancer. (Olivo et al., 2010) notes that immunotherapy is not a universal solution and its effectiveness varies depending on the cancer type and individual patient characteristics. Genetic testing of the tumor can sometimes help predict whether a patient is likely to respond to immunotherapy. Immunotherapy can be expensive, and insurance coverage may vary. The long-term effects of some immunotherapies are still being studied.

Conclusion: It's essential to discuss the potential benefits and risks of immunotherapy with your oncologist. They can help determine if immunotherapy is appropriate for your specific situation and explain the potential side effects and other considerations.

Cycle Specific and Cycle Nonspecific Drug:

The cell cycle is the way a cell copies itself to make more cells. This happens in phases.

- Resting Phase(G_0: Nothing is happening)
- G_1 Phase (Gap-1: A growth phase)
- S Phase (Synthesis: When copying of DNA happens)
- M Phase (Mitosis: When one cell splits into two cells)

Cycle specific drug: These drugs kill cancer cells only during a certain phase and are not able to work in the resting phase.

Cycle-nonspecific drug: These drugs kill cancer cells during any phase of the cell cycle.

Mathematical model in Cycle Specific Chemotherapy:

We discuss the Mathematical model provided by Panetta, J., & Adam, J. (n.d.). *A Mathematical Model of Cycle-Specific Chemotherapy* [8].

A mathematical model is like a recipe that uses numbers and equations to describe how things work in the real

world. In this case, it helps scientists understand how chemotherapy affects tumors.

A two-dimensional linear differential equation is a type of math equation that helps describe changes over time in two different areas. In this context, it looks at how the tumor and the chemotherapy interact over time. Imagine you are tracking two things, like the amount of medicine in the body and the size of the tumor. This equation helps show how one affects the other. Periodically pulsed chemotherapy means that the medicine is given in bursts or pulses at regular intervals.

The model mentioned in the text is similar to earlier work done by researchers named Eisen and Schiller [9] . They created a two-compartment model, which means they looked at two different areas or groups of cells in the tumor.

Another group of researchers, Birkhead [10] and others, expanded on this idea by adding more complexity. They included resistant compartments, which are parts of the tumor that do not respond to treatment. This made their model more complicated, with four different areas to consider.

Two-Compartment Model in Tumor Growth [8]

A two-compartment model is a way to represent the behavior of tumor cells in two different states: cycling and non-cycling.

- Cycling cells are actively dividing and growing, while non-cycling cells are not currently dividing.

The equation given here is a mathematical representation of how these two types of cells interact.

$$\begin{pmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \end{pmatrix} = \begin{pmatrix} \alpha - \mu - \eta & \beta \\ \mu & -\beta - \gamma \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \ldots\ldots(1)$$

The equation includes several parameters, which are constants that help define the behavior of the cells:

α – (cycling cells growth rate): This is how fast the cycling cells are growing. A higher value means they grow faster.

μ – (rate of cycling cells becoming non-cycling): This is how quickly cycling cells stop dividing and become non-cycling.

Think of it as workers taking a break.

η – (natural decay of cycling cells): This represents how many cycling cells die naturally over time.

β – (rate of non-cycling cells becoming cycling): This is how quickly non-cycling cells start dividing again and become cycling cells.

γ – (natural decay of non-cycling cells): This is how many non-cycling cells die naturally. This parameter is optional, meaning it may not always be included.

The vector (x_1, x_2) represents two types of tumor cells:

x_1 : This is the mass of cycling tumor cells. These are the cells that are actively dividing and growing.

x_2 : This is the mass of non-cycling tumor cells. These cells are not actively dividing; they are in a resting state.

Assumptions Made in the Model: The model makes some important assumptions:

- Positive Net Growth Rate: The assumption that $\alpha > \eta$ means that if there is no chemotherapy, the tumor will keep growing indefinitely.

This is like saying if the factory keeps hiring workers, it will keep producing more products.

- Large Number of Cells Moving to Non-cycling: The assumption that $\alpha - \mu - \eta < 0$ indicates that many cycling cells are becoming non-cycling.

According to Birkhead et al., [10] only about 20% of the tumor cells are cycling. This means that most of the tumor cells (80%) are not actively dividing. If you have 100 tumor cells, only 20 of them are actively growing, while 80 are resting.

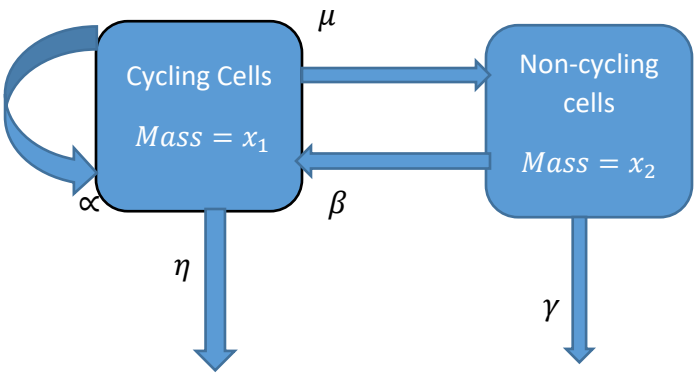
To simplify the model, let $a = \alpha - \mu - \eta \quad and \quad \gamma = 0$.

Then the system becomes:

$$\frac{d\bar{x}}{dt} = \begin{pmatrix} -a & \beta \\ \mu & -\beta \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \ldots\ldots\ldots\ldots (2)$$

Where $a, \alpha, \mu \geq 0$. Birkhead et al., [10] provided specific values for these parameters based on data from breast cancer studies:

- α = 0.5: This indicates a certain growth rate of cycling cells.
- μ= 0.218: This represents the rate at which cells move to the non-cycling state.
- η= 0.477: This is another growth-related parameter.
- β= 0.05: This could represent a rate of cell death.



A two-compartment diagram, which visually represents the cycling and non-cycling cells. Imagine two boxes. One box has the cycling cells, and the other box has the non-cycling cells. Arrows between the boxes show how cells can move from one box to another.

Periodic Chemotherapy:

Periodic chemotherapy refers to giving cancer treatment in cycles. This means

that the treatment is not continuous but happens at specific times.

Cycle-Specific Chemotherapy:

Cycle-specific chemotherapy means that the drugs used in treatment only target cells that are actively dividing or "cycling." Cancer cells often grow and divide quickly, so these drugs are designed to attack them when they are most vulnerable.

Types of Chemotherapeutic Effects:

There are two types of effects from chemotherapy. We will focus on the first one, which is called a "pulsing condition."

Pulsing Condition:

A pulsing condition means that the chemotherapy drugs are given in bursts or pulses [11] . In this case, the drugs kill a certain number of cancer cells instantly during each treatment period. This means that every time the treatment is given, it has an immediate effect on the cells that are dividing at that moment.

The pulse periodic condition represented mathematically as:

$$\overline{x_{n\tau^+}} = \begin{pmatrix} f(D) & 0 \\ 0 & 1 \end{pmatrix} \overline{x_{n\tau^-}} \text{.....(3)}$$

This is a mathematical equation that shows how certain variables change over time during chemotherapy treatment.

$\overline{x_{n\tau^+}}$: This represents a state or condition of the system (like the tumor or cells) at a specific time. The n could refer to a specific cycle of treatment, while $\tau+$ indicates a time point after a certain event (like a dose of chemotherapy).

$\overline{x_{n\tau^-}}$: This is similar to the previous vector but refers to the state of the system just before the event, at time $\tau-$. It helps us understand how the system was before the treatment was applied.

The 0's in the matrix indicate that there is no direct effect from one part of the system to another in that specific way. The 1 means that the second part of the system remains unchanged. This could represent a stable aspect of the cells that is not affected by the chemotherapy.

$f(D)$: This is a function that depends on D, which could represent a dose of chemotherapy. The function $f(D)$ tells us how effective the chemotherapy is at that specific dose. In simple terms, it tells us how many cancer cells survive after being treated with a specific amount of medicine [11].

Also Birkhead et.al [10] examine $0.05 \leq f(D) \leq 0.4$. This means that the survival fraction of the cells can be between 0.05 and 0.4. This means that after treatment, at least 5% of the cancer cells survive, and at most 40% survive.

For piece wise continuous case, Equation(2) can be modified as:

$$\frac{dx}{dt} = \begin{pmatrix} -a & \beta \\ \mu & -\beta \end{pmatrix} \bar{x} - \begin{pmatrix} g(t) & 0 \\ 0 & 0 \end{pmatrix} \bar{x} \text{.....(4)}$$

This describes how certain quantities change over time. In this case, it relates to the behavior of cancer cells under the influence of chemotherapy.

$\frac{dx}{dt}$ indicates how the vector $\bar{x}$ changes over time (denoted by t).

$-a$ represents the rate at which cancer cells die due to chemotherapy. A higher value of a means more effective treatment.

β indicates the rate at which healthy cells might be affected by the chemotherapy, potentially leading to side effects.

μ represents the rate at which healthy cells can be affected by the presence of cancer cells.

$g(t)$: The function g(t) is a special type of mathematical function called a piecewise continuous function. This means that the function is defined in different pieces or sections, and it is continuous within those sections. In this context, g(t) describes how chemotherapy affects a tumor over time.

Webb [12] used a step function to model the effects of chemotherapy. A step function is like a staircase; it stays flat for a while and then jumps up or down suddenly. This is different from the smooth changes we see in g(t). By comparing this model with Webb's, the authors aim to show how their approach might be more realistic or useful in understanding chemotherapy effects.

In this mathematical model, authors will use a specific type of function called the exponential decay function to describe the effects of chemotherapy.

This function is written as:

$$g(t) = he^{-\gamma(t-n\tau)};\ \ n\tau \le t < (n+1)\tau$$

Here, h is a cell kill parameter, which tells us how effective the chemotherapy is at killing cancer cells. The larger the value of h, the more cells are killed.

The symbol γ represents the decay of the drug, which means how quickly the drug loses its effectiveness over time.

The variable t represents time. The function g(t) is only valid during certain time intervals, specifically between $n\tau$ and $(n+1)\tau$ Here, n is an integer (like 0, 1, 2, etc.), and τ is a fixed time period.

The authors note that, like Webb's model, g(t) can take on many different forms. This means that the function can be adjusted or changed based on what is most appropriate for the situation. For example, if a different type of chemotherapy is used, the function might look different to better represent how that drug works.

Relation between Cycle Specific Chemotherapy and Exponential Decay Function:

What is Cycle-Specific Chemotherapy?

- Cycle-specific chemotherapy refers to a type of cancer treatment that targets cancer

cells during specific phases of their growth cycle.

- Cancer cells grow and divide in a cycle, and different drugs work best at different times in this cycle.
- By timing the administration of chemotherapy drugs to coincide with these phases, doctors can maximize the effectiveness of the treatment.

Why Use a Mathematical Model?

- Researchers use mathematical models to predict how cancer cells will respond to chemotherapy over time.
- These models help in understanding the best doses and timing for the drugs to achieve the best results.
- The goal is to find the optimal period for treatment that leads to the most significant reduction in tumor size.

What is an Exponential Decay Function?

- An exponential decay function is a mathematical way to describe how something decreases over time.
- In the context of chemotherapy, it can represent how the number of cancer cells decreases after treatment.
- The function shows that the rate of decrease is proportional to the current amount, meaning that as the number of cancer cells decreases, the rate of decrease also slows down.

How Does Exponential Decay Work?

- Imagine you have a jar of jellybeans, and every hour, you eat half of the jellybeans left in the jar.
- After the first hour, you have half the jellybeans. After the second hour, you eat half of what remains, and so on.
- This pattern of eating jellybeans illustrates exponential decay: the amount decreases quickly at first but slows down as fewer jellybeans are left.

Importance of Understanding Exponential Decay in Chemotherapy:

- By understanding how cancer cells die off over time, doctors can better plan treatment schedules.
- This knowledge helps in determining how often to give chemotherapy and how much to give each time.
- It also allows researchers to explore how other factors, like growth factors, can enhance the effectiveness of chemotherapy.

Examples of Growth Factors:

- Growth factors are substances that can stimulate cell growth and division.
- In chemotherapy, certain growth factors can help make cancer cells more sensitive to the drugs, leading to a more effective treatment.
- For instance, if a growth factor is introduced during a specific phase of the cancer cell cycle, it may help the chemotherapy drug work better.

Conclusion:

- Cycle-specific chemotherapy and the use of mathematical models, like the exponential decay function, are crucial in the fight against cancer.
- By understanding these concepts, researchers and doctors can improve treatment strategies, leading to better outcomes for patients.
- The ongoing study of these models and their applications continues to enhance our understanding of how to effectively combat cancer.
- Understanding how chemotherapy works through these models helps doctors make better decisions about treatment plans.
- By knowing how different types of chemotherapy affect tumors, doctors can choose the
- best approach to shrink the tumor and improve patient outcomes.
- This research can lead to more effective treatments and potentially save lives.
- Doctors can use the findings to decide how much chemotherapy to give to patients.
- The goal is to find the dose that kills the most cancer cells while keeping the patient as healthy as possible.

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